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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/729,454	12/04/2000	Amy W. Lasek	PC-0028 US	6223

27904 7590 11/27/2002

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/27/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,454	LASEK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-21* is/are pending in the application.

4a) Of the above claim(s) *9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: seq. alignment

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Election/Restrictions

The prosecution history indicates applicant elected group I drawn to DNA, with species SEQ ID NO:1 (SEQ ID NO:1 is not a DNA, but protein) with traverse (see Paper NO:5), and claims 3, 9-20 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention in the Office Action mailed 10/23/01. Claim 3 was rejoined with the elected group in the Office Action mailed Office Action mailed on 06/04/2002 because SEQ ID NO:3 encodes SEQ ID NO:1.

Claims 1-4, 6-21 are pending and claims 9-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claims 1-4, and 6-8 are examined on merits.

Claim Rejections - 35 USC § 112

Claims 1-4, an 6-8 **remain rejected** for reasons set for the in the two previous Offices mailed 10/21/2001 and 06/04/2002 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. After reading the applicant's argument (Paper No.11) at pages 6-11, it is apparent that two issues, i.e., **enablement** and **written description** under 35 U.S.C. 112, first paragraph are addressed in the amendment. The instant claims are drawn to a polynucleotide encoding a protein which has undetermined function or biological significance and the claims were rejected in the Office Action mailed on 10/23/2001 because it would take undue experimentation to use the invention in colon cancer diagnosis (Note page 4, paragraphs 5 and 6 in the Office Action mailed on 10/23/2001); cancer diagnosis using a biomarker such as the instant invention is not a trivial matter (unpredictable). This rejection was maintained in the next Office Action because applicant argument was not persuasive.

Applicant in the amendment (Paper NO.11) mainly argues that claims are amended to recite the limitation "at least 90% amino acid sequence identity" to SEQ ID NO:1 to expedite prosecution and further argues that the instant claims specifically define the claimed genus through the recitation of chemical structure, therefore the genus claimed in instant claims are predictable in the current state of art; these argument will be addressed later under written description requirement. See New Grounds of Rejection infra under Written Description section.

The enablement under 35 U.S.C. 112, first paragraph is addressed in this part of the instant Office Action. The instant specification does not guide one skilled in the art to use the instant invention in colon cancer diagnosis.

The specification discloses:

1) At Table 2, the instant invention is expressed in both normal and all other diseased colon tissues and the expression is not specific to any specific colon disease.
2) At Table 5 (data obtained with micoarray analyis), 1st row, Dn4097 does not have colon cancer according to the specification at page 39, lines 26 and 27 under Tissue Samples, where it says that Donor 4097 has gastric cancer, not colon cancer. Further, it is apparent that data at Table 5 was not obtained using age, sex unmatched normal controls.

The specification does not teach how to diagnose colon cancer or any other cancer for the matter by using the instant invention because expression level of SEQ ID NO:3 is about the same in both normal and cancerous colon tissues at table 2 (compare row 5 and 7 with 8) and the data at Table 5 could be interpreted as within normal range expression, less than two-fold decrease in colon tumors compared with control not matched with sex or age. The data at Table 5 do not give enough guide to one in skilled to use the instant invention in colon cancer diagnosis without undue experimentation in light of unpredictability in art for diagnosing cancer using ***a*** biomarker expression in microarray. For example, Marx et al (9-8-200, Science vol. 289 pages 1670-2) teaches at the last three paragraphs of the article that lack of standardization makes it difficult to relate the findings of the different labs and assess their quality of

microarray data. Therefore based on less than 2-fold change compared with sex, age unmatched control, one in skilled in art would doubt that the information in Table 5 could be used in colon cancer diagnosis without undue experimentation. For example, if the expression level of the instant invention is, let say, five-fold decrease in one patient compared with pooled colon tissue sample, is that finding indicative of colon cancer? How about if the expression level change is 1.5 fold decrease by a different microarray system and different analysis software than the inventor used?

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach cancer diagnosis using biomarker is not a trial matter and further teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to instant invention. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). As the summary of the specification above indicates the specification does not teach if the proteolytic

fragment could be used as a biomarker for potential tumorigenicity detected in blood or any other in vivo medium surrounding the cells.

Undue experimentation is required to determine if difference in expression level of the instant invention is associated with human cancer. This process requires analyzing of a large clinical samples, namely primary tumor samples and compare them with age and sex-matched normal controls to determine whether the change in expression level of the instant invention is associated with human colon cancer.

Considering lack of examples of diagnosing a colon cancer and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

The rest of the species in the instant claims other than SEQ ID NO:3 encoding SEQ ID NO:1 also remain rejected for the reasons set forth at paragraph numbers 7-9 of the Office Action mailed on 10-23-2001 and also for the reasons set forth at Paragraph 1 at page 2 of the Office Action mailed on 6-4-2002. The following is reiteration of the two previous Office Actions. The specification does not teach how to use the various polynucleotide molecules other than SEQ ID NO:3. The specification does not say whether other species other than SEQ ID NO:3 also could be used in colon cancer detection. The specification does not disclose any data concerning all other species except SEQ ID NO:3 encoding SEQ ID NO:1. Applicant argues that the other species could be used as probe for unspecified purpose. However, this argument is not persuasive because it is not clear how to use the rest of the claimed species for "a real world use" without undue experimentation.

Claim Rejections - 35 USC § 102

Claims 1, 4, 6 - 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Boll et al (IDS, 1993, J. Biol. Chem. vol. 268, pages 12901-12911). Based on applicant's amendment (Paper No. 11) at page 12, explaining what is meant by the limitation "an antigenic epitope of SEQ ID NO:1 recited in claim 1, the claims rejection is reinstated.

The Claim are drawn to an isolated mammalian cDNA comprising a sequence encoding an antigenic epitope of SEQ ID NO:1, a composition comprising the cDNA, a probe comprising the cDNA, a vector comprising the cDNA, and a host cell comprising the cDNA.

Applicant says at page 12 of the amendment (Paper NO. 11) that that limitation "an antigenic epitope" is a fragment or portion of SEQ ID NO:1 and defined in the specification as a portion or fragment of a larger protein at page 9 lines 29-30 and page 10 lines 7-10. Applicant further says that antigenic epitope is well known in the art and the art definition of the limitation is about 5 amino acids in length. Note page 293 of Levinson at al (1994, Medical Microbiology and Immunology, 3rd edition, Appleton & Lange). Therefore the limitation "an antigenic epitope of SEQ ID NO:1" is interpreted as any five consecutive amino acids of SEQ ID NO:1.

The following rejection is a reiteration of the Office Action mailed on 10/23/2001: Boll et al (1993, J. Biol. Chem. vol. 268, pages 12901-12911, copy provided with the Office Action mailed 10/23/2001) teach an isolated mammalian (i.e, rabbit) cDNA comprising a sequence encoding an antigenic epitope of instant SEQ ID NO:1, a composition, a probe, a vector comprising the cDNA: Note Material and Methods section at page 12901-3, Figs 1-3. Note the attached sequence alignment also. Thus the claims reads on the cDNA taught by Boll et al.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 c) is confusing, therefore indefinite. Is a fragment from nucleotide number 160 to 200 of SEQ ID NO:3 within the metes and bounds of the limitation in claim 3 c)?

Claims1, 3, 4, 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. The claims are interpreted as drawn to genus of cDNA, i.e. SEQ ID NO:3, and allelic variants and splicing variants of SEQ ID NO:3, wherein the variants encode proteins with at least 90 % sequence identity to SEQ ID NO:1. The specification provides evidence for SEQ ID NO: 3 only. Since the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants adequately describes SEQ ID NO:3. Applicant in the amendment (Paper NO.11) argues that claims are amended to recite the limitation "at least 90% amino acid sequence identity" to SEQ ID NO:1 to expedite prosecution and further argues that the instant claims specifically define the claimed genus through the recitation of chemical structure, therefore the genus claimed in instant claims are predictable in the current state of art. However, this argument is not persuasive because it is apparent that applicant did not have **possession** of the entire claimed invention other than SEQ ID NO:3 at the time of filing the instant application.

Claim Rejections - 35 USC § 102

Claims 1, 3, 4, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by NCBI accession number AI833131 (7-13-1999).

The claim are interpreted as drawn to a fragment of DNA per se from encoding antigenic epitope of SEQ ID NO:1 and DNA fragment in claim 3 c). NCBI accession number AI833131 (7-13-1999) teaches a fragment of DNA encoding an antigenic fragment of SEQ ID NO: 3 and the fragment specified in claim 3 c. Compare the instant Figure 1E and 1F to the DNA sequence of NCBI accession number AI833131. Note the sequence alignment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
November 25, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600